REVISED COMMENTS ON THE 1986 SURGEON GENERAL'S REPORT, THE EPA DRAFT RISK ASSESSMENTS, THE NIOSH CURRENT INTELLIGENCE BULLETIN, AND OTHER RISK ASSESSMENTS ON ETS

The conclusions of reports by three governmental agencies have been extensively relied upon by various organizations and individuals in discussions of health effects purportedly associated with environmental or "passive" tobacco smoke (ETS) exposure in the workplace. These reports are:

[1] The Health Consequences of Involuntary Smoking,[1] a 1986 report of the Surgeon General (hereinafter 1986 Surgeon General's Report);

[2A] Health Effects of Passive Smoking: Assessment of Lung Cancer in Adults and Respiratory Disorders in Children (EPA/600/6-90/006A),[2A] a review draft released by the Environmental Protection Agency (EPA) in 1990 (1990 Draft Risk Assessment);

[2B] Respiratory Health Effects of Passive Smoking: Lung Cancer and Other Disorders (EPA/600/6-90/006B),[2B] a review draft released by the Environmental Protection Agency (EPA) in 1992 (1992 Draft Risk Assessment); and

[2C] Respiratory Health Effects of Passive Smoking: Lung Cancer and Other Disorders (EPA/600/6-90/006F),[2C] a risk assessment released by the Environmental Protection Agency (EPA) on January 7, 1993 (Final Risk Assessment); and

[3] Environmental Tobacco Smoke in the Workplace: Lung Cancer and Other Health Effects,[3] a Current Intelligence Bulletin issued by the National Institute for Occupational Safety and Health in 1991 (NIOSH CIB).

These reports have taken on importance in the context of the OSHA RFI to the extent that OSHA RFI commenters may try to rely upon these documents (and other published risk assessments, also discussed herein) in urging OSHA to regulate smoking in the workplace. As underscored in the following comments, these review papers do not provide a basis for regulation of smoking in the workplace by OSHA.

1986 Surgeon General's Report

The EPA draft risk assessment and the NIOSH CIB rely extensively on the conclusions of the 1986 Surgeon General's Report on "Involuntary Smoking," the U.S. Public Health Service's eighteenth report, and the fifth report issued during the tenure of C. Everett Koop. The 1986 Surgeon General's Report reached

two major conclusions which some may urge are relevant to the workplace smoking issue:

> Involuntary smoking is a cause of disease, including lung cancer, in healthy nonsmokers. (p. vii)
>
> The simple separation of smokers and nonsmokers within the same air space may reduce, but does not eliminate, the exposure of nonsmokers to environmental tobacco smoke. (p. vii)

The Surgeon General's review has been challenged by a number of critics. One reviewer, Ann Fettner, suggested that the Surgeon General's conclusions were based on "flimsy" evidence presented in an effort to "divert our attention" from important health concerns such as the "poisoning of the environment."[4] A U.S. Congressman, Walter B. Jones, in a letter published in the Congressional Record, wrote that "the conclusions in the Surgeon General's Report are not supported by the research in his own report."[5] The Surgeon General's conclusions regarding lung cancer, cardiovascular disease, adult respiratory disease, and separation of smokers and nonsmokers are relevant to OSHA's current considerations of the workplace environment and will be discussed below in some detail.

Lung Cancer

The Surgeon General's conclusion that a causal relationship exists between ETS exposure and lung cancer in nonsmokers was based on 13 epidemiologic studies of women whose husbands smoked. Of those studies, eleven reported risk estimates that were not statistically significant.[6] Moreover, scientific deficiencies in the epidemiologic studies on ETS and nonsmoker lung cancer have been identified by numerous individuals. A German specialist in biometrics and epidemiology, Karl Uberla, in his assessment of these studies, suggested that the data fail to meet the criteria which some regard as necessary to establish a causal relationship:[7]

> The majority of criteria for a causal connection are not fulfilled. There is no consistency, there is a weak association, there is no specificity, the dose-effect relation can be viewed controversially, bias and confounding are not adequately excluded, there is no intervention study, significance is only present under special conditions and the biologic plausibility can be judged controversially.

An eminent American statistician, Nathan Mantel, has also observed:[8]

> [I]t is unlikely that any epidemiological study has been, or can be, conducted which could permit establishing that the risk of lung cancer has been raised by passive smoking. Whether or not the risk is raised remains to be taken as a matter of faith according to one's choice.

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There are currently 30 spousal smoking studies, 24 of which report risk estimates that are not statistically significant.[9-38] Only six studies report statistically significant increased lung cancer risks for women whose husbands smoke. Thus, these studies taken as a group, or considered individually, do not convincingly support rejection of the null hypothesis of no association between ETS exposure and lung cancer in nonsmokers, and therefore are inadequate as a basis for regulatory action.

Moreover, the vast majority of the spousal smoking studies report risk estimates that are less than 2.0. These values are at the limit of detection for epidemiology. Risk estimates below 2.0 or 3.0 have been described as "weak," and thus, any conclusions drawn from such studies are unreliable.[39] This is particularly true when the studies themselves fail to account for numerous sources of bias and confounding factors. The confounding factors are variables associated with both the classification of "marriage to a smoker" and with risk factors associated with lung cancer, the existence of which can give rise to a spurious ETS-lung cancer association. Examples of confounding factors that are not controlled for in the studies include diet, alcohol consumption, cooking and heating methods, occupation, physical activity, urbanization and socioeconomic class.[40]

In addition, application of spousal smoking studies to the workplace presents significant questions. Even the Surgeon General conceded that "[m]ore accurate estimates for the assessment of exposure in the home, workplace, and other environments are needed" (p. 101).

In fact, the epidemiologic studies on lung cancer and respiratory disease cited in the Surgeon General's Report did not include any actual measurements of study subjects' exposure to ETS in either the home or the workplace. Instead, the studies relied on questionnaire information to estimate exposure to ETS. The Surgeon General's Report itself acknowledges that the "possibility of reporting bias must be considered for the studies that have used questionnaires to measure illness experience" (p. 38). A number of researchers have reported that exposure misclassification can lead to improper indices of exposure and incorrect estimations of risk.[10,41-46] The Surgeon General's Report also concedes that "validated questionnaires are needed for the assessment of recent and remote exposure to environmental tobacco smoke in the home, workplace, and other environments" (p. 107). The National Research Council and other authors have recently criticized questionnaires used in ETS studies for not being standardized or validated, pointing out that misclassification of exposure may occur if the questionnaire is not appropriately designed.[47-49]

Separation of Smokers and Nonsmokers

The Surgeon General's Report also concluded that "simple separation of smokers and nonsmokers within the same air space may reduce, but does not eliminate, exposure of nonsmokers to environmental tobacco smoke" (p. vii). The Report concludes that smoking bans will not only reduce ETS exposures, but will also "alter smoking behavior and public attitudes about tobacco use" (p. 322). The Report further suggests that "over time, this may contribute to a reduction of smoking in the United States" (p. 322). Thus, the underlying motivation for the use of the ETS/health argument is to attain a "smoke-free society by the year 2000."

The Surgeon General's claim that separation of smokers and nonsmokers does not minimize nonsmoker exposure to ETS is without scientific support. Studies aboard commercial aircraft and in offices indicate, contrary to the Surgeon General's Report, that the simple separation of smokers and nonsmokers effectively minimizes nonsmoker exposure to ETS.[50-57] One recent study, for example, reported that the use of designated smoking areas reduced exposure to ETS by 95 percent.[50] Another study of a smoking-restricted office building reported that ambient nicotine in nonsmoking areas was virtually undetectable, suggesting that ETS had a negligible impact on the nonsmoking areas in the building.[51]

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In addition, Canadian researchers Sterling, et al., in a series of studies, collected data on levels of ETS constituents in offices with different smoking policies. They reported no significant differences in average ETS constituent levels between nonsmoking offices that received recirculated air from designated smoking areas and nonsmoking offices that did not receive recirculated air.[52-53,57] They concluded:

> The results indicate that the provision of a designated, but not separately ventilated smoking area can effectively eliminate or drastically reduce most components of environmental tobacco smoke from nonsmoking offices.

Adult Respiratory Disease

The Surgeon General's Report also addressed purported changes in pulmonary function in adults reportedly exposed to ETS. The Surgeon General concluded that

> healthy adults exposed to environmental tobacco smoke may have small changes on pulmonary function testing, but are unlikely to experience clinically significant deficits in pulmonary function as a result of exposure to environmental tobacco smoke alone. (p. 13)

Two major research groups have examined the possible association between exposure to ETS in the workplace and pulmonary function in adult nonsmokers. White and Froeb reported, based on

their measurements of the small airways function of smokers and nonsmokers in the workplace, that nonsmokers exposed to tobacco smoke at work for 20 or more years had reduced function of the small airways compared to nonsmokers who did not have such exposures.[58]

The White and Froeb study has been criticized for numerous reasons, including its assessment of ETS exposure and its method of subject selection.[59-62] Furthermore, White and Froeb themselves noted that the average values of the pulmonary tests of nonsmokers exposed to tobacco smoke "were not notably different" from the values suggested as normal by a specialist in this area.[63] Dr. Michael Lebowitz of the University of Arizona wrote the following regarding the White and Froeb study:[64]

> Even with a biased population, poor study design, and incorrect statistical evaluation, there were no clear-cut, consistent, medically meaningful differences between passive smokers and groups of nonsmokers; a corrected statistical analysis strengthened this conclusion.

Moreover, the Surgeon General wrote:

> The [White and Froeb] study population was self-selected, and the exposure classification was crude and did not account for people who changed jobs. (p. 60)

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In addition to these concerns, the results of White/Froeb appear to be inconsistent with those of a second research group, Kentner, et al., who reported no effect of ETS on pulmonary function measurements among 1,351 German office workers.[65] In a 1988 update of the study, Kentner and colleagues noted that[66]

> there is no evidence that average everyday passive smoke exposure in the office or at home leads to an essential reduction of lung function in healthy adults.

The key investigator for the study reported these same findings in 1989 and 1990 publications.[67,68]

The Surgeon General's Report also addressed the issue of acute effects on the pulmonary function of adult nonsmokers exposed to ETS, the Surgeon General concluded that "the magnitude of these changes is quite small, even at moderate to high exposure levels, and it is unlikely that this change in airflow, per se, results in symptoms" (p. 63). The studies available on asthmatic adults are clinical studies that have potential applicability to the home and the workplace setting. However, the studies that have reported an association between exposure to ETS and reactions in asthmatics have several problems. Regarding the studies on asthma in adults, the Surgeon General wrote:

> Acute exposure in a chamber may not adequately represent exposure in the general environment.

> Biases in observation and the [sic] in selection of subjects and the subjects' own expectations may account for the widely divergent results. Studies of large numbers of individuals with measurement of the relevant physiologic and exposure parameters will be necessary to adequately address the effects of environmental tobacco smoke exposure on asthmatics. (p. 65)

Cardiovascular Disease

The Surgeon General's 1986 conclusion on cardiovascular disease and ETS was that further studies "are needed in order to determine whether involuntary smoking increases the risk of cardiovascular disease" (p. 14). In 1988, Fielding, et al., reviewers from the University of California-Los Angeles, who are critical of smoking, conceded that "no firm conclusion that a causal relation exists is yet warranted" for reported ETS exposures and cardiovascular disease.[69] A similar view was expressed in a 1988 review from a Harvard physician, who said that there were "no clear data" that ETS increases heart disease risk.[70]

Several additional evaluations of the literature on ETS and heart disease appeared in 1990. Two of these were reported at international conferences in Lisbon, Portugal[71] and in Budapest, Hungary.[72] Both argued strongly that the data on ETS and heart disease were methodologically weak and insufficient to draw conclusions. In another major review, this one from the United States, two physicians, Drs. Mahajan and Huber, concluded that

"the data that are available are so sparse that any attempt to reach a definitive assessment would be fraught with uncertainty."[73] Perhaps the most recent review of the literature on ETS and heart disease was published in 1991 by A.K. Armitage, the former director of toxicology of a major European research laboratory.[74] He described the scientific data relating to a possible heart disease risk in nonsmokers exposed to ETS as "not very convincing."

In summary, the Surgeon General's claims that exposure to ETS increases the risk of lung cancer in nonsmokers and that simple separation of smokers and nonsmokers is ineffective in minimizing exposure are not convincingly supported by the scientific data and should not be used as a basis for workplace smoking policy decisions.

EPA Draft Risk Assessment

In June, 1990, the United States Environmental Protection Agency (EPA) released for review a Draft Risk Assessment on ETS.[2A] The 1990 Draft Risk Assessment concluded that exposure to ETS is causally related to lung cancer in adult nonsmokers and is associated with respiratory disease and respiratory symptoms in children. The 1990 Draft Risk Assessment also concluded that ETS should be classified as a Group A ("known human") carcinogen. It estimated that ETS exposures are responsible for 3,800 nonsmoker

lung cancer deaths per year in the U.S. (the estimate was later revised to 3,700). The Science Advisory Board (SAB) for the EPA reviewed the 1990 Risk Assessment in a meeting in December, 1990. Their report, presented to the SAB Executive Committee in April, 1991, suggested that while further revisions were needed, the conclusions of the Draft were sound.

In May, 1992, the EPA released its revised Draft Risk Assessment on ETS.[2B] The revised Draft Risk Assessment again concluded that exposure to ETS is causally related to lung cancer in adult nonsmokers. The revised Draft also concluded that ETS exposures are causally related to respiratory diseases and symptoms in children and added numerical estimates of risk for various respiratory conditions. The revised Draft Risk Assessment again concluded that ETS should be classified as a Group A ("known human") carcinogen. However, the EPA lowered its estimated number of U.S. lung cancer deaths purportedly attributable to ETS exposure to 3,000 per year. This revised Draft Risk Assessment was reviewed by the EPA's SAB Committee in July, 1992. More charges for revisions were made to the EPA staff, but the committee once again endorsed the Draft's conclusion. An Executive Committee meeting of the EPA-SAB took place in October, 1992. The Executive Committee endorsed the SAB committee's report, and the Draft was sent back to EPA staff for minor revisions.

On Thursday, January 7, 1993, at a press conference, EPA Administrator William Reilly and Secretary Sullivan of the Department of Health and Human Services released the final EPA document, entitled, "Respiratory Health Effects of Passive Smoking: Lung Cancer and Other Disorders."[2C] The document classifies ETS a Group A ("known human") carcinogen. This is apparently the first EPA risk assessment based solely upon epidemiologic data in which a substance has been designated a Group A carcinogen.

All three versions of the EPA Risk Assessment employ a Population-Attributable Risk model for estimating excess lung cancer mortality among nonsmokers reportedly exposed to ETS.[2A,2B,2C] This model is based essentially upon three estimates:

1. a point estimate or relative risk derived from a meta-analysis of epidemiologic studies on nonsmoking wives married to smokers;
2. the proportion of nonsmokers in the general (U.S.) population reportedly exposed to ETS; and
3. the total number of nonsmokers in the general population.

To calculate the Population-Attributable Risk (PAR), the authors of the 1990 Draft Risk Assessment estimated that 60% of all nonsmokers are exposed to ETS. A cumulative relative risk of 1.28 was calculated in the 1990 Draft via meta-analysis from epidemiologic studies on spousal smoking as the estimated excess

risk due to ETS exposure. The PAR for these two assumptions (with other minor adjustments) is 0.27. The total number of deaths for nonsmoking males and females was then estimated, based on the American Cancer Society's projections for 1988 (9,500 total deaths). By multiplying the PAR (0.27) by 9,500, the authors generated an estimate of 2,560 total deaths per year attributable to ETS exposure among neversmokers. A PAR was also computed for male and female former smokers, generating a total estimate of 3,800 excess deaths annually purportedly attributable to ETS exposure among nonsmokers in the United States. Using the same procedure in the 1992 Draft, the authors performed a meta-analysis of the then available eleven U.S. spousal smoking studies and reported a relative risk of 1.19. The calculated cumulative risk generates an estimate of 3,000 excess deaths per year among nonsmokers. The EPA did not modify its 1992 Draft estimate in the final risk assessment document.

The PAR method employs estimates of relative risk, population fractions of exposure to ETS and lung cancer death rates for the general nonsmoking population in order to generate an estimate of excess mortality reportedly attributable to ETS exposure. It is important to note at the outset that the PAR model itself does not determine that there is an increased risk of lung cancer among nonsmokers from ETS exposure. Rather, the model assumes a causal relationship between ETS exposure and an increased risk of lung cancer among nonsmokers, based upon increased risks

reported in epidemiologic studies on spousal smoking. These reported relative risks are, in turn, assumed to represent true relative risks for the entire population due to ETS exposure.

These critical assumptions have been challenged.[75] To achieve a cumulative excess risk estimate of 1.28 for nonsmokers reportedly exposed to ETS, the authors of the 1990 Draft Risk Assessment performed a meta-analysis of 23 epidemiologic studies on spousal smoking. Eighteen of the studies on spousal smoking included in the EPA's meta-analysis in 1990 fail to achieve statistical significance and are, therefore, consistent with the null hypothesis of no association between spousal smoking and an increased risk of lung cancer among nonsmokers.

The meta-analysis in the 1992 Draft was performed on eleven available U.S. spousal smoking studies, none of which originally reported an overall statistically significant risk estimate. Nevertheless, the EPA reanalyzed the data, using 90% confidence intervals, and reported statistical significance for one risk estimate. The EPA's meta-analysis generated a summary risk estimate of 1.19 for nonsmoker lung cancer. Using a 90% confidence interval, the EPA reported that this risk estimate was statistically significant and that it indicated a causal relationship between spousal smoking and nonsmoker lung cancer. The EPA justified their choice of the 90% confidence interval by referring to a "one-tailed"

statistical test. The one-tailed test presumes causation: it is designed to show the extent of a purported "effect."

The choice of confidence interval was criticized in a presentation at the October SAB Executive Committee meeting, by James J. Tozzi. In a follow-up letter to the EPA, Tozzi included a meta-analysis of 13 U.S. studies which is not statistically significant using a 95% confidence interval.[76] Tozzi reported a relative risk of 1.07 (95% C.I.: 0.95 to 1.21). Nonetheless, the EPA did not choose to modify their statistical calculations in the final risk assessment document. The main difference between the meta-analysis submitted by Tozzi and the EPA meta-analysis was that the analysis submitted by Tozzi included two recent lung cancer studies that did not report an overall association between spousal smoking and lung cancer in nonsmoking wives. The EPA omitted from its risk assessment the NCI-funded Brownson et al., 1992, study, one of the largest and most recent studies on ETS and lung cancer, which found no increase in risk from exposure to ETS.[77] They also omitted the Stockwell et al., 1992, study.[78] If the EPA had included the Brownson and Stockwell studies in its meta-analysis, its risk assessment would not have resulted in a statistically significant increased risk of nonsmoker lung cancer reportedly associated with exposure to ETS.

Eleven of the epidemiological studies EPA considered in the 1992 Draft Risk Assessment included estimates of workplace exposures. Ten of those eleven studies reported no statistically significant increased risk for nonsmoking females. If the data on workplace exposures are pooled in a meta-analysis, the risk estimate is below 1.00 (unity), which indicates no positive association between reported workplace exposures to ETS and lung cancer in nonsmokers. However, the Draft Risk Assessment did not consider those important data. It also excluded from its analysis published criticisms of epidemiologic studies on spousal smoking and lung cancer. The EPA additionally excluded from consideration over 25 studies on childhood respiratory disease and parental smoking which did not report an effect from parental smoking.

The epidemiologic studies on spousal smoking contain no actual exposure data on ETS. The 1990 and 1992 EPA Drafts instead assumed the validity of questionnaire responses about possible exposure to ETS based upon spousal smoking and then generalized these responses to the general population's exposure to ETS. The authors of the 1990 and 1992 Draft Risk Assessments also failed to consider and adequately adjust for confounding factors, e.g., diet, lifestyle, genetics, etc., in any of the individual studies on spousal smoking. This is a significant oversight, especially when dealing with "weak" relative risks which approximate 1.3 in the 1990 Draft Risk Assessment and only 1.19 in the 1992 Draft. When dealing with relative risks this small, spurious associations may

be reported between two factors. For example, because the EPA did not adequately address the potential role of diet, there is a chance that the association the EPA reported between ETS exposure and nonsmoker lung cancer may actually be a result of a common association the two factors may have with poor diet.

The Draft's assumption of causality is based upon tenuous data from epidemiologic studies on spousal smoking. The assumption is the critical element to the PAR model and the original estimate of 3,800 (and revised estimate of 3,000) excess nonsmoker deaths per year reportedly due to ETS exposure. The 1990 and 1992 Draft Risk Assessments fail to argue convincingly for the assumption. Without the causal assumption, the PAR approach is little more than an exercise in mathematical modeling.

The conclusions of the 1990 Draft Risk Assessment were strongly criticized, particularly in many of the more than 100 comments submitted during the public comment period on the draft.[75] Specifically, many of the public comments found EPA's classification of ETS as a Group A carcinogen to be scientifically unwarranted.

One point of criticism was that the EPA's proposed classification of tobacco smoke as a "human carcinogen" was based in part upon the imputed identification and presence in ETS of suspected carcinogens reported in mainstream smoke and/or fresh

sidestream smoke. However, the EPA apparently did not review the available published data on either the characterization of, or exposure to, ETS. ETS is neither chemically nor physically equivalent to either mainstream or sidestream smoke, and it is therefore not scientifically acceptable to treat ETS, mainstream smoke and sidestream smoke as qualitatively and quantitatively similar mixtures.[79-84]

As discussed above, meta-analysis, a statistical procedure which combines the reported risk estimates from a number of studies to generate an overall estimate of risk, was used in the EPA's Population-Attributable Risk model. The problems and limitations of the use of meta-analysis for epidemiologic studies have been addressed in the scientific literature.[85,86] For instance, meta-analysis does not account for intrinsic bias and confounding in the individual studies, and it cannot remedy study design flaws. As two German scientists, Heinz Letzel and Karl Uberla, noted: "Combining risk estimates from biased or confounded studies by meta-analysis cannot provide correct answers."[86] The spousal smoking studies used in the 1990 meta-analysis were conducted in the United States, Europe and Asia. These populations differ genetically and in lifestyle factors, and the studies themselves differ in design.[85] The 1992 Draft included separate meta-analyses for the different countries and regions.

Another major criticism of the 1990 Draft Risk Assessment was that in addition to its inadequate treatment of the data on the physical and chemical properties of ETS, it also virtually ignored the available exposure data, toxicological data and data from animal studies on ETS. The 1992 Draft similarly failed to consider these data. For instance, not one of the spousal smoking studies included actual measurements of ETS exposure; exposure was only estimated by responses to questionnaires. However, a large body of literature exists on actual measurements of ETS in indoor environments, which was not considered in the 1990 Draft Risk Assessment and only cursorily considered in the 1992 Draft.[52,79,87-90] While these data are independent of the epidemiologic literature, they suggest that nonsmoker exposure to ETS in typical public places and workplaces is minimal.[52,87-90] For example, some studies report typical measurements of nicotine ranging from an exposure equivalent of 1/100 to less than 1/1,000 of one filter cigarette per hour.[56,91-97]

While a docket for written comments was not established for the 1992 Risk Assessment, oral comments were allowed at both the July SAB committee and the October Executive Committee meetings. However, commenters were asked not to reiterate previous points of discussion. One major issue raised by Dr. William J. Butler in July was the EPA's treatment of confounders.[98] The EPA took the position that confounders could not account for the reported

association between spousal smoking and nonsmoker lung cancer, since the EPA was unable to find a single confounding factor that could consistently account for the results reported in all of the studies used in the Draft Risk Assessment. Butler criticized the EPA's position and stated that there were many potential confounders that should be considered important, and that it was not necessary (or even reasonable to expect) to identify a single confounder that would apply to all of the individual studies.

Finally, if the EPA had followed its own 1986 guidelines for carcinogen risk assessment, it would have included: (1) a hazard evaluation which would have examined data regarding the physical and chemical characterization of ETS, as well as the results from published animal inhalation studies and in vitro studies; (2) an exposure evaluation which would have included the data from well over 100 studies in the published literature which monitored ETS constituents in the air of public places and workplaces; (3) a dose-response evaluation which would have included an examination of the actual data reported in the epidemiologic studies on spousal smoking; and (4) a risk characterization which would have included the range of uncertainty in numbers of lung cancer deaths reportedly attributable to ETS exposures. The guidelines also require that chance must be ruled out statistically in all epidemiologic studies under consideration

and that all possible biases and possible confounding factors are to be considered.

Thus, the conclusions of the EPA's 1990 and 1992 Draft Risk Assessments are based on an incomplete and selective review of the existing data on ETS. Several of the public comments on the 1990 Draft suggested that this amounted to EPA's apparent failure to follow its own guidelines for carcinogen risk assessment.[75] In fact, the EPA would not have classified ETS as a Group A carcinogen had the EPA used the methodologies and guidelines it employed in all its previous risk assessments.

NIOSH Current Intelligence Bulletin

In June 1991, NIOSH released Current Intelligence Bulletin 54 on environmental tobacco smoke.[3] The NIOSH CIB stated that:

> NIOSH has determined that the collective weight of evidence (i.e., that from the Surgeon General's reports, the similarities in composition of MS and ETS, and the recent epidemiologic studies) is sufficient to conclude that ETS poses an increased risk of lung cancer and possibly heart disease to occupationally exposed workers. (p. 12)

In the excerpt above, the CIB refers to three areas that contribute to its "collective weight of evidence." The Surgeon

General's report is the first area; however, the conclusions of the Surgeon General's report have been extensively criticized, as discussed above. As for the second type of "evidence" (the claimed "similarities in composition of MS and ETS"), the treatment of the available data in the NIOSH CIB is neither detailed nor complete.

Although the NIOSH CIB and the EPA Draft Risk Assessment stress the reported association between active smoking and disease in reaching their conclusions about ETS, neither report provides detailed discussions of the chemical and physical natures and differences between ETS and mainstream smoke (MS). ETS is different in both quality and quantity from both mainstream and sidestream smoke. (See Responses to Questions 2a(iii) and 35.)

One major area overlooked by both the NIOSH CIB and the EPA Draft Risk Assessment is those scientific studies that actually measured levels of ETS constituents in indoor air. There is a substantial body of literature in this area which is directly relevant to considerations about non-industrial workplace exposure. If the actual data on ETS exposures in the workplace are examined, one finds that typical workplace exposures to ETS are minimal and often below limits of detection for even the most sensitive tobacco smoke constituent monitors. (See Response to Question 2a(iii).)

The final aspect of NIOSH's "weight of the evidence" is "recent epidemiologic studies" on ETS and lung cancer. However, its review of the spousal smoking studies is incomplete. The CIB states that eight additional spousal smoking studies have been published since 1986, when, actually, 14 have been published, most of which report associations which do not achieve statistical significance. Furthermore, the CIB acknowledges serious shortcomings in the available epidemiologic studies purporting to relate ETS exposure and lung cancer:

> NIOSH recognizes that these recent epidemiologic studies have several shortcomings: lack of objective measures for characterizing and quantifying exposures, failure to adjust for all confounding variables, potential misclassification of ex-smokers as nonsmokers, unavailability of comparison groups that have not been exposed to ETS, and low statistical power.

Nevertheless, the CIB uses spousal smoking studies to reach its conclusion about occupational exposure to ETS without justifying the relevance of spousal smoking studies to workplace exposure. Of the spousal smoking studies, none actually measured levels of ETS to which the subjects ostensibly were exposed. The NIOSH CIB also fails to address the 12 spousal smoking studies that included specific questions about workplace exposure.[9-20] Of those studies, ten reported no statistically significant increased risk of lung cancer for nonsmokers who reported ETS exposure in

the workplace. The other two studies presented risk estimates which were of borderline statistical significance. Thus, the epidemiologic data are consistent with the null hypothesis, i.e., that there is no association between workplace ETS exposure and nonsmoker lung cancer.

The CIB also purports to review the studies on ETS and heart disease that have appeared since 1986, at which time the Surgeon General remarked that more studies were needed before a conclusion of an association could be made. While additional studies have been published since 1986, taken as a whole, the studies still do not allow a conclusion to be reached.[99] Moreover, the epidemiologic studies on ETS and heart disease may be criticized for several reasons: they use spousal smoking as a surrogate for ETS exposure, they do not have clinical diagnoses of heart disease (e.g., they rely on death certificate data or self-reported symptoms), and they fail to adequately account for confounding factors. The latter include family history of heart disease, blood pressure, serum lipoprotein levels, body mass index, age, menopausal status, dietary fat, alcohol consumption, diabetes and lifestyle factors (e.g., a sedentary lifestyle).

Thus, the NIOSH CIB, which reaches conclusions about purported risks associated with exposure to ETS in the workplace, is not a comprehensive, critical review of the available data.

Of even greater significance, it does not address available workplace data on exposures or potential health effects.

Other Risk Assessments on ETS

Two basic methods (modeling procedures) for estimating the population risk for lung cancer among nonsmokers reporting exposure to ETS have appeared in the scientific literature. The first method, adopted by the U.S. EPA in its Draft Risk Assessment (discussed above), is the Population-Attributable Risk (PAR) approach. A PAR model seeks to establish an estimate of excess risk due to ETS exposure and is expressed as a ratio of the risk assessed for ETS to the total lung cancer risk for nonsmokers from all sources. The PAR is calculated by applying a relative risk estimate associated with reported exposure to ETS (derived from risk rates in epidemiologic studies) to the percentage of individuals believed to be exposed to ETS in the general population.

A second approach used in the literature, called the Extrapolation Method (also called the Linear Extrapolation Method or Dose-Response Extrapolation Model), combines reported risks of lung cancer for active smokers, derived from epidemiologic studies on smokers, with estimates of tobacco smoke exposure (dose) for active smokers. The risk and dose estimates for active smokers are then extrapolated downward to apply to nonsmokers. The

estimated excess risk for nonsmokers exposed to ETS is obtained by dividing the lung cancer risk reported for active smokers by the ratio between the smokers' and nonsmokers' estimated average exposure to tobacco smoke.

This second approach for estimating excess lung cancer deaths among nonsmokers reportedly due to ETS exposure is exemplified by the model developed by Repace and Lowrey (1985).[100] The authors employed a linear downward extrapolation from the lung cancer risk reported for active smokers (and estimates of tobacco smoke exposure for smokers) to an exposure and residual risk estimate for nonsmokers allegedly exposed to ETS. The model estimated lung cancer mortality among nonsmokers by dividing the reported lung cancer risk for active smokers by a ratio of estimated tobacco smoke exposure for smokers and nonsmokers. The linear dose-extrapolation model therefore requires four estimates:

1. the number of nonsmokers supposedly exposed to ETS;
2. the average ETS exposure of nonsmokers;
3. the average tobacco smoke exposure for active smokers; and
4. the lung cancer risks reported for current active smokers.

Specifically, Repace and Lowrey developed a version of a linear dose-response extrapolation model which is based upon a

weighted average of nonsmoker exposure to particulates. The weighted average estimate was not derived from actual exposure data but from a model which predicts ambient concentrations of particulate matter from the number of cigarettes smoked in a given volume of air space. The authors also calculated a lung cancer risk estimate and an estimate of daily "tar" (particulate) intake for active smokers. Nonsmoker risk of lung cancer was extrapolated from those estimates to yield 555 lung cancer deaths per year attributable to ETS exposure among nonsmokers.

Arundel, et al., (1987) refined the Repace and Lowrey extrapolation model by replacing Repace and Lowrey's estimates of particulate matter exposure for nonsmokers with actual exposure data from monitoring studies.[101] The Arundel, et al., model also rejected Repace and Lowrey's extrapolation from the dose of active smokers to the exposure of nonsmokers, and replaces the latter with an estimated retained dose of particulates for nonsmokers. Using virtually the same assumptions as Repace and Lowrey, the Arundel et al. model estimates 12 lung cancer deaths per year among 40 million male and female neversmokers.

The various assumptions and estimates employed in the Repace and Lowrey linear dose-extrapolation model have been challenged by a number of scientists.[101-105] One scientist noted that the exposure and dose levels Repace and Lowrey used were not

based on actual measurements, and that actual measurements reported by other researchers ranged from "ten-to-one-hundred-fold less than that in the Repace and Lowrey model."[102]

Still other scientists have questioned the methods of analysis used in their article.[103-105] For example, the Repace and Lowrey extrapolation model assumes that the carcinogenicity of tobacco smoke depends upon some (unknown) element purportedly located in the particulate phase of ETS. The model also assumes that lung cancer per unit of exposure (i.e., per mg of "tar") is the same for mainstream smoke and ETS, an assumption which is not borne out by the scientific data regarding the chemistry of mainstream smoke and ETS. Moreover, the extrapolation model suggests that the relationship between reported risk and level of exposure is linear (i.e., dose-response), and it assumes that there is no exposure level below which lung cancer risk is absent. The dose-extrapolation model also assumes, with its suggestion of a linear dose-response from active smoking to low level exposure to ETS, that the so-called "one-hit" cancer theory, a theory that one molecule of exposure to a suspected carcinogen is sufficient to induce carcinogenesis, is valid. However, the "one-hit" model has what statisticians call a "zero intercept term," which is equivalent to assuming that lung cancer risk among nonsmokers is zero <u>in the absence of ETS</u>.

Even with its dubious assumptions and estimates, it is noteworthy that the linear dose-extrapolation model produces estimates of excess lung cancer deaths which are roughly an order of magnitude lower than estimates generated by the PAR model which relies on epidemiologic studies. A number of subsequently published extrapolation models, unlike that of Repace and Lowrey, have been based upon actual data and reasonable estimates of exposure.[101,106-108] These models have been unsuccessful in estimating any appreciable increased risk of lung cancer for nonsmokers reporting exposure to ETS. Indeed, extrapolation models based on estimates of retained particulate matter generate estimates of excess risk which are as much as 20 orders of magnitude lower than estimates generated by the PAR method. Such vast ranges underscore the difference between risk estimates based on epidemiology and those based on dosimetry. This difference is so striking that even the authors of the EPA Draft Risk Assessment were unable to generate a "dose-response based on the extrapolation from mainstream to environmental tobacco smoke," and hence, relied solely upon the PAR model to support their contention of an increased risk of lung cancer among nonsmokers reportedly exposed to ETS.[109]

There have been two published risk assessments of environmental tobacco smoke (ETS) exposure and heart disease, the first by A. Judson Wells in 1988,[110] and the second by Kyle

Steenland in 1992.[111] However, despite his never having published a risk assessment on ETS and heart disease, Stanton Glantz is the individual most often cited for the conclusion that a large number of annual heart disease deaths in the U.S. are attributable to ETS exposure. In a 1991 article with William Parmley,[112] Glantz claimed that the number of annual ETS-related nonsmoker deaths in the U.S. is approximately 53,000, the largest portion of which (37,000) he claimed was from heart disease.

The figure of 53,000 annual U.S. deaths attributed to ETS exposure originated in a publication by A. Judson Wells in 1988,[110] although Wells actually argued for a "best estimate" of ETS related deaths that was somewhat lower, about 46,000, with 32,000 of these due to heart disease. Stanton Glantz and William Parmley repeated the 53,000 figure in their 1991 article in Circulation. However, they did not themselves independently perform a calculation of "excess" deaths, but instead relied on the earlier work by Wells, which is cited by Glantz and Parmley as the basis for their claim.

To calculate excess deaths due to ETS exposure, Wells used meta-analysis to derive ETS-associated relative risks for lung cancer, heart disease and cancers other than the lung. These relative risks, together with an estimate of the fraction of the population exposed to ETS, were entered into an equation that was used to calculate excess death rates for never smokers. To derive

a value of actual numbers of deaths related to ETS exposure, these excess death rates were multiplied by the number of people in the U.S. estimated to be exposed. Based on such calculations, Wells estimated that ETS exposure produced 39,000 excess deaths per year in the U.S.

Further calculations attempted to take into account misclassification, either of smokers as nonsmokers or of nonexposed nonsmokers as exposed to ETS. Wells calculated that these adjustments for misclassification resulted in a revision upward of the estimate, from 39,000 to 53,000. Wells then stated that a more "conservative" estimate would be 46,000, a value chosen because it is halfway between the unadjusted value of 39,000 and the adjusted value of 53,000.

It is clear that the claim of 53,000 excess deaths associated with ETS exposure is assailable at every level of its derivation. At the most fundamental level, the studies contributing to the meta-analysis are scientifically flawed. The flaws stem from, among other reasons, small sample sizes, inadequate control for potential confounding factors and unreliable estimates of ETS exposure. Such flaws contribute to the invalidity of the subsequent meta-analysis, a technique which is further called into question because it is not designed to bring together such methodologically disparate studies. Furthermore, any overall estimate of the

prevalence and levels of ETS exposure within the U.S. is based on assumptions, rather than direct measurement. In addition, a variety of other unproven assumptions are made in attempting to adjust the data to take potential misclassification into account. Finally, the seemingly capricious derivation of the annual death rate claim is reflected in Wells' final calculation in which he decided, based on no particular formula, that the value of 46,000 would be a "best estimate," simply because it was halfway between an unadjusted and adjusted estimate. Such loose and unscientific conclusions should not form a basis for regulatory action.

Kyle Steenland, a National Institute for Occupational Safety and Health employee, also performed a risk assessment of ETS and heart disease, published in 1992.[111] He calculated that 35,000-40,000 annual U.S. heart disease deaths are attributable to ETS exposure. He concluded that "heart disease mortality is contributing the bulk of the public health burden imposed by passive smoking."

There are two important differences between Steenland's estimation process and that used by Wells. First, Steenland did not do a meta-analysis to obtain a pooled estimate of relative risk for heart disease mortality associated with ETS exposure. Instead, he simply adopted the relative risk reported in a single study of a Maryland sample[113] and applied that to the entire U.S.

population. Second, he focused only on heart disease and did not attempt to calculate ETS-related deaths from other diseases.

Other than the above, Steenland's procedure for calculating deaths attributable to ETS exposure was generally similar to that reported by Wells. This estimation process involved: positing an overall increase in relative risk of heart disease associated with ETS exposure; making adjustments for potential misclassification and for background exposure; estimating the extent of exposure to ETS; and estimating the fraction of nonsmoker heart disease deaths attributable to ETS exposure. These estimates were incorporated into a formula using data on U.S. heart disease death rates and population estimates, from which was derived an estimated number of annual heart disease deaths attributed to ETS exposure. According to Steenland's calculations, "the overall estimate of ETS-attributable heart disease deaths for never-smokers and former smokers is 35000 to 40000." He further commented that these increased risks of death "are higher than those accepted in regulating environmental toxins."

Steenland's calculations involved problems similar to those that plagued Wells' attempt to derive a number of deaths associated with ETS exposure. Although Steenland cannot be criticized for performing an invalid meta-analysis (because he did no meta-analysis at all), his procedure can perhaps be criticized

even more severely because he took a relative risk based on a single study from a single county in a single state and applied it to the United States as a whole. Criticisms relating to unverified assumptions, which were noted in regard to Wells' calculations, also apply to Steenland's procedure.

Summary

The conclusions of these governmental reports and other publications are extensively relied upon by those who claim that there is a possible association between ETS exposure in the workplace and adverse health effects in nonsmokers. However, these reports and assertions have serious deficiencies that make their conclusions difficult to support. When appropriate scientific scrutiny is exercised, these reports and articles do not provide a defensible basis for the regulation of smoking in the workplace by OSHA.

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